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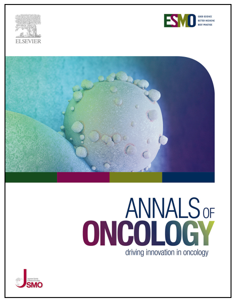

Immunogenicity and early clinical outcome after two or three doses of SARS-CoV-2 mRNA-BNT162b2 vaccine in actively treated cancer patients: results from the prospective observational Vax-On-Third study.

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PII: S0923-7534(22)00674-3

DOI: https://doi.org/10.1016/j.annonc.2022.04.002

Reference: ANNONC 903

To appear in: *Annals of Oncology*

Received Date: 1 February 2022

Revised Date: 8 March 2022

Accepted Date: 3 April 2022

Please cite this article as: Nelli F, Giannarelli D, Fabbri A, Silvestri MA, Giron Berrios JR, Virtuoso A, Marrucci E, Schirripa M, Mazzotta M, Onorato A, Panichi V, Topini G, Pessina G, Natoni F, Signorelli C, Chilelli MG, Primi F, Ruggeri EM, Immunogenicity and early clinical outcome after two or three doses of SARS-CoV-2 mRNA-BNT162b2 vaccine in actively treated cancer patients: results from the prospective observational Vax-On-Third study., *Annals of Oncology* (2022), doi: https://doi.org/10.1016/j.annonc.2022.04.002.

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Immunogenicity and early clinical outcome after two or three doses of SARS-CoV-2 mRNA-BNT162b2 vaccine in actively treated cancer patients: results from the prospective observational Vax-On-Third study.

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KEYWORDS

COVID-19, tozinameran, third dose, cancer, anticancer therapy, immunogenicity

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The SARS-CoV-2 variants of concern (VOC) widespread and breakthrough infections prompted additional preventive measures in fully-vaccinated immunocompromised recipients, including actively treated cancer patients[1]. Regulatory agencies recommended a third homologous (booster) dose of an mRNA-based vaccine for this condition based on evidence from immunosuppressed organ transplant recipients[2]. This study aimed to evaluate the safety, immunogenicity, and clinical outcome of two or three doses of BNT162b2 vaccine (tozinameran) in patients with solid malignancies receiving systemic therapies.

The Vax-On-Third is a prospective, observational study that included adult cancer patients on active treatment within the previous six months and who had completed a two-dose schedule of tozinameran 26 to 22 weeks before enrollment. COVID-19 infection at any time was an exclusion criterion. Patients who received booster dosing (Boost-cohort) compared with those who did not (Unboost-cohort) for different reasons (Supplementary Figure S1). All enrolled patients were tested for IgG antibody titer against receptor binding domain of SARS-CoV-2 Spike protein (RBD-S1) at baseline (timepoint-1) and four weeks after the third dose (timepoint-2). We used the SARS-CoV-2 IgG II Quant immunoassay on the ARCHITECT i2000sr automated platform (Abbott, Sligo, Ireland) with a cut-point ≥50 AU/mL indicating a positive seroconversion response. A threshold ≥4446 AU/ml was selected as a correlate of 50% vaccine efficacy (VE) against symptomatic COVID-19 infection[3]. The incidence of SARS-CoV-2 infections was monitored in both study cohorts by periodic swab testing. Dedicated safety questionnaires were delivered at timepoint-1 and collected at timepoint-2. Propensity score matching (PSM) was performed to reduce potential selection bias between the cohorts. Proper two-sided tests were applied with a significance level P<0.05 for each comparison within the matched population (Supplementary Statistical Analysis). The study followed STROBE reporting guidelines and was approved by the referring Ethics Committee (protocol number: 1407/CE Lazio1; clinical study identifier: EudraCT number 2021-002611-54).

We enrolled 372 consecutive patients between September 23 and October 7, 2021 (Supplementary Figure S1 and Table S1). All patients were evaluable for safety, while 253 (98.1%) cases in the Boost-cohort completed serologic testing at timepoint-2. Systemic adverse events were mostly mild to moderate and did not exceed 15% of cases, with only four patients (1.6%) reporting severe reactions (Supplementary Table S2). After PSM, 91 patients in Boost-cohort and 158 patients in Unboost-cohort were included in the comparative analysis, with no significant differences in confounding factors between the groups. (Supplementary Table S1). Median anti-RBD-S1 IgG titer [Unboost-cohort: 296 AU/mL (95% CI 187-460) vs Boost-cohort: 454 AU/mL (95% CI 359-584; P=0.078], seroconversion rate (Unboost-cohort: 86.8% vs Boost-cohort: 89.9%; P=0.46), and 50%

VE rate (Unboost-cohort: 4.4% vs Boost-cohort: 6.3%; *P*=0.52) did not differ between cohorts at timepoint-1. The third dose of vaccine resulted in an exponential increase in median anti-RBD-S1 IgG titer [15024 AU/mL (95%CI 11598-19447)], which was significantly higher than assessment at timepoint-1 in both Unboost- (*P*<0.001) and Boost-cohort (*P*<0.001). Accordingly, seroconversion rate (99.4%, *P*<0.001) and 50% VE rate (76.9%, *P*<0.001) improved significantly in the same comparison (*P*<0.001, Figure 1B and 1C). After a median follow-up of 145 days (IQR 140-153), 18 patients in the Unboost-cohort (19.8%) and 10 in the Boost-cohort (6.3%, *P*=0.001) reported contracting SARS-CoV-2 infection, none of which was clinically severe. On multivariate analysis, only immunosuppressive corticosteroid therapy and ECOG-PS2 correlated significantly with an impaired antibody response at timepoint-2 (Supplementary Table S3).

This cohort study confirms a favorable safety profile of the third dose of tozinameran in a broad sample of cancer patients receiving active treatments. While residual confounding may still be present, comparative evaluation within the PSM population suggests improved immunogenicity of booster dosing, independent of types and timing of systemic therapies and consistent with similar studies that employed the same serologic testing methodology[4-5]. Although longer follow-up is required, the effects of booster vaccine dosing appear to translate into a reduced risk of infection during intense SARS-CoV-2 VOC outbreaks.

ACKNOWLEDGEMENTS

All authors express their gratitude to the Strategic Directorate of Viterbo Public Health Agency, whose unselfish commitment made the conduct of this research project possible.

FUNDING

None declared.

DISCLORURE

The authors have declared no conflicts of interest.

Abbreviations: RBD-S1, receptor binding domain of SARS-CoV-2 Spike protein; PSM, propensity score matching.

Timepoint-1; antibody response assessment six months after starting vaccination for both cohorts; Timepoint-2; antibody response assessment four weeks after the third dose of tozinameran; Unboost-cohort; patients who did not receive the third dose of tozinameran six months after beginning vaccination schedule; Boost-cohort; patients receiving the third dose of tozinameran six months after beginning vaccination schedule.

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Legends

Figure 1. Antibody response after two or three doses of tozinameran vaccine within PSM population.

A. Comparison of scatter plot distributions and medians of anti-RBD-S1 IgG titers (logarithmic values).

Bars represent median values with Interquartile Range.

B. Comparison of seroconversion response rates at cut-off ≥50 AU/mL

C. Comparison of 50% vaccine efficacy response rates at cut-off ≥4446 AU/mL

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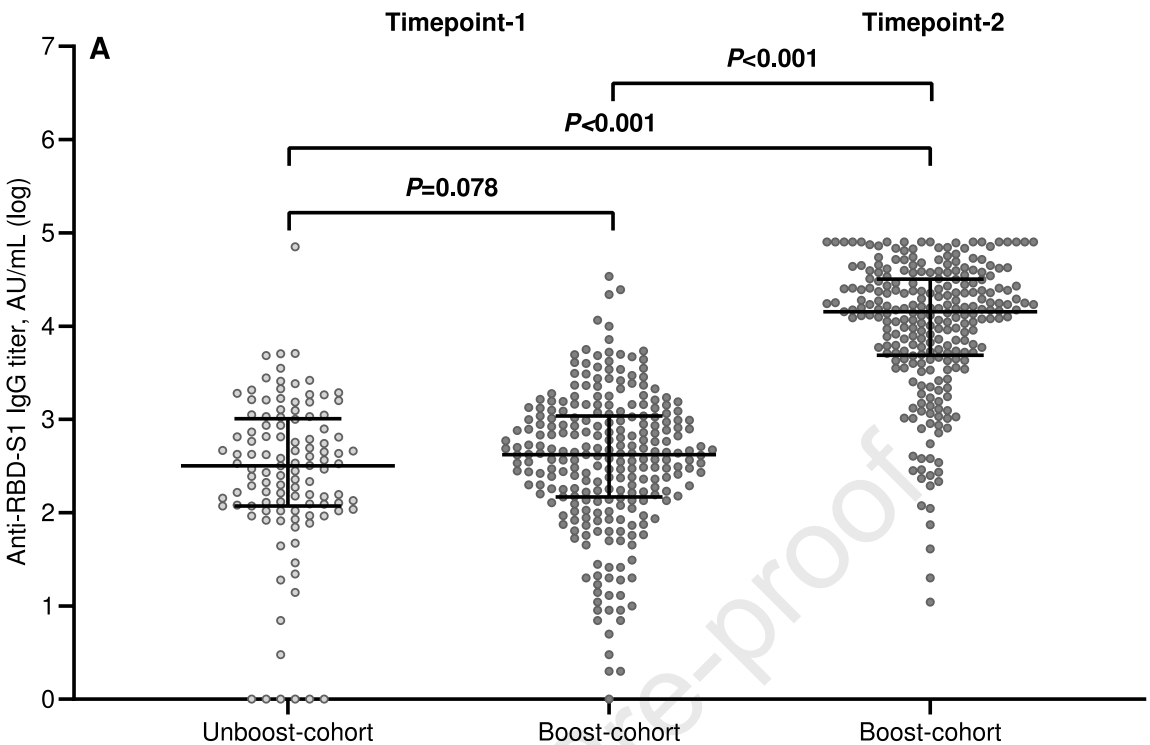
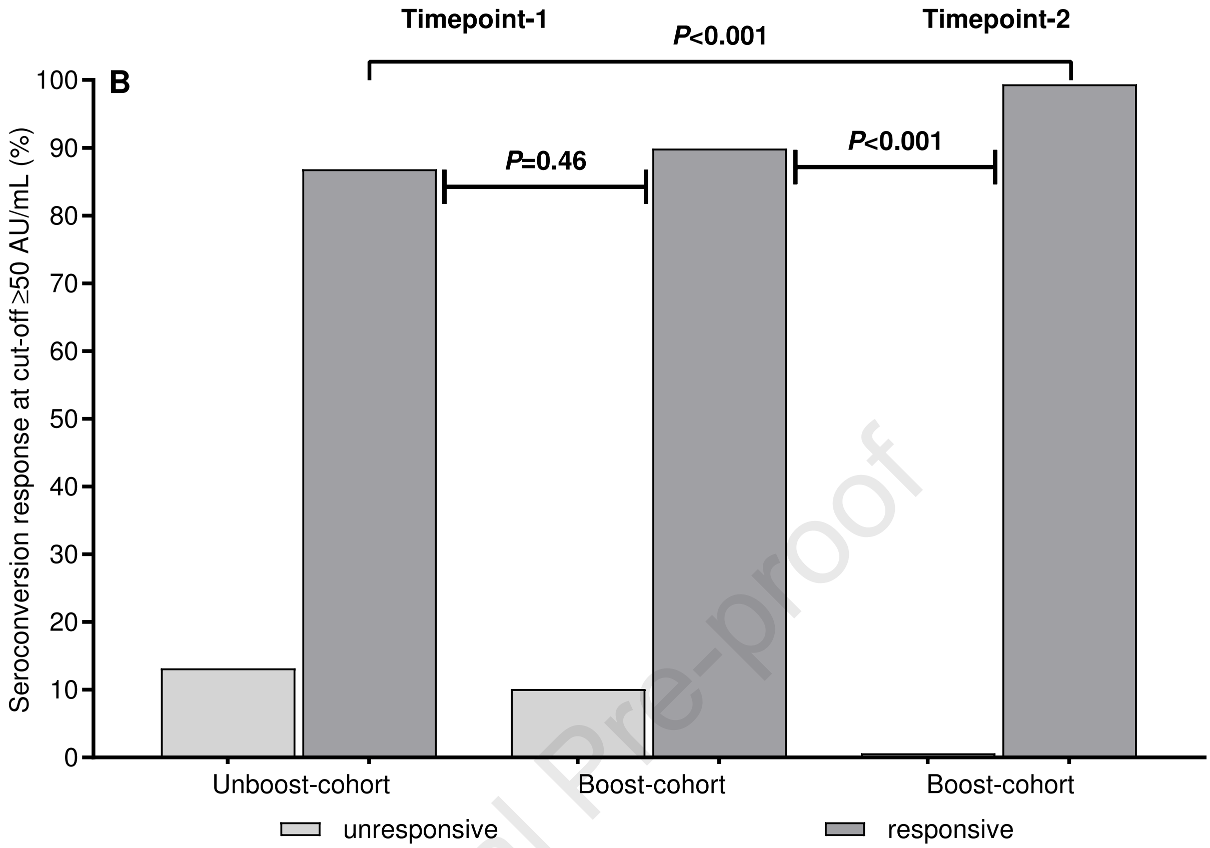


Timepoint-1
Timepoint-2
A
P<0.001
P<0.001
P=0.078
Anti-RBD-S1 IgG titer, AU/mL (log)
0
1
2
3
4
5
6
7
Unboost-cohort
Boost-cohort
Boost-cohort



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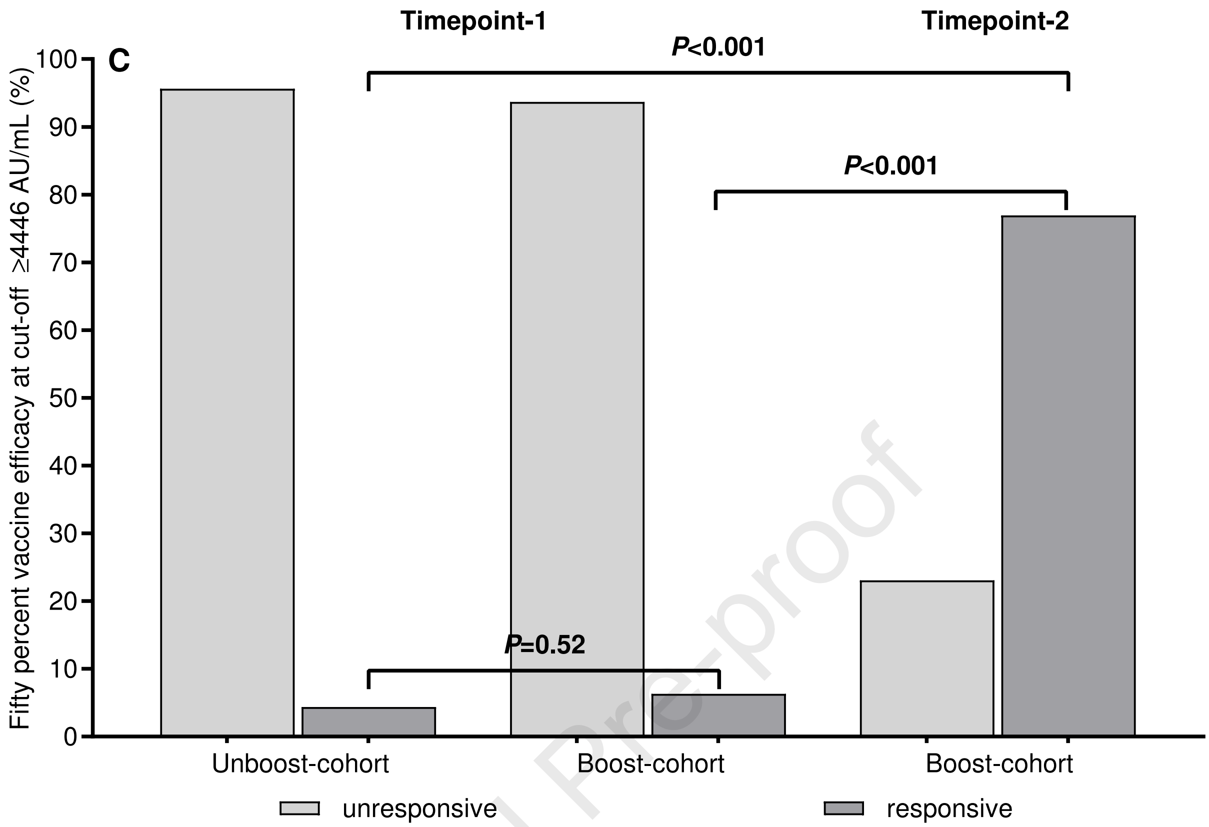

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